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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

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PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PIR Rev. No. [illegible]: Review of Chronic Toxicity Study of Fenpropathrin Technical in Dogs. Accession No. 071117.

TO: Mr. Timothy A. Gardner, PM Team #12
Registration Division

FROM: Karen L. Hamernik, Ph.D., Toxicologist
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Tox. Chem. File No. 7F2

Attached is a review of a 52-week chronic toxicity study of technical grade S-3206 (fenpropathrin, active ingredient) in Beagle dogs, submitted by the sponsor, Sumitomo Chemical Co., Ltd.

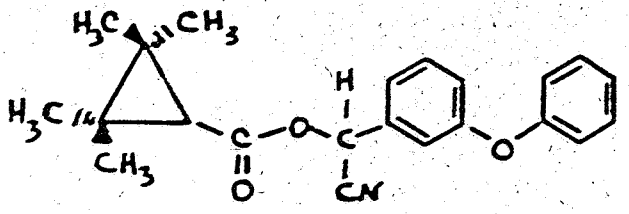
Comments and conclusions concerning the study may be found at the end of the review. The study was classified as Core Minimum.

The dog chronic toxicity study was submitted in support of an FIFRA/ temporary tolerance request for the use of fenpropathrin on apples and pears. However, copies of the experimental use permit petition, the temporary tolerance petition, and the proposed product label were not provided with this submission. Therefore, Toxicology Branch will not deal with nor discuss these issues in this memo.

52-WEEK CHRONIC TOXICITY STUDY OF TECHNICAL GRADE S-3206 (Fenpropathrin, active ingredient) IN BEAGLE DOGS. This study was conducted at Hazleton Laboratories America, Inc., Vienna, Virginia, under the direction D. H. Pence, Ph.D., from February 3, 1983 to February 6, 1984 (Hazleton Project No. 343-153). Final report date: November 12, 1984. The study sponsor was the Sumitomo Chemical Company, Ltd., Osaka, Japan. EPA Numbers: [illegible], Record 135795, Accession 073113, Tox. Chem. File 27H.

MATERIALS

Test Material: The material tested, S-3206, technical grade, Lot No. 20514, was described as a brown solid. S-3206 contains, as the active ingredient, fenpropathrin (chemical name - alpha-cyano-3-phenoxybenzyl-2,2,3,3-tetramethyl cyclopropanecarboxylate), at 92.5% purity by weight (see structure below).



Fenpropathrin

Test Animals: The 16 male and female Beagle dogs selected for the study were obtained from Hazleton Research Animals, Inc., Cumberland, Virginia. Upon receipt and prior to the study's initiation, animals were quarantined for at least three weeks. When the study commenced, animals were five to eight months old and no animals were reported to have been unhealthy at that time.

Test Groups: Dogs of each sex were ranked by weight and were then randomly assigned to one of four treatment groups.

Husbandry: Animals were each uniquely numbered with an ear tag and were individually housed in stainless steel cages. During the study, a 12/12 hour light-dark cycle of artificial lighting was maintained and room temperature was monitored daily. Animals were given free access to tap water and feed (Ground Wayne® Lab Dog Diet), which depending on the test group, did or did not contain test material. The feeding apparatus used was not described and specific details about how food was administered to test animals were not provided. Both the basal feed and the drinking water were analyzed for contaminants but of those found, none were believed by the study authors to have compromised the study results (analysis reports were not submitted).

Test Diets: Control animals received basal diet alone. Diets containing test material were prepared by mixing a pre-determined amount of S-3206 with basal feed. The homogeneity and stability of S-3206 admixed in each type of diet was assessed by analytical chemical methods, prior to the start of the study. During the study, diets were freshly prepared and administered to the animals each week. At weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, samples of all four diets were taken in order to analyze the concentration of S-3206 present.

METHODS

Protocol: For a period of 52 weeks, four dogs per sex per dose were given free access to either 0 ppm, 100 ppm (low-dose), 250 ppm (mid-dose), or 750 ppm

(high-dose) of S-3206 admixed in their diet. All animals surviving the study were terminated after week 52 and a necropsy was performed both on these animals and on the animal which died while the study was in progress.

Parameters Examined:

Clinical signs. Examinations for morbidity and mortality of test animals were conducted twice daily. Once daily, the behavior, fecal elimination, and appearance of each dog was checked and the presence of any toxicological or atypical signs were noted.

Body weights and food consumption. Animal body weights were recorded the day the study started and thereafter, the body weight and food consumption (kg food/week) of each animal was monitored weekly for weeks 1 through 16 and then once every fourth week for the remainder of the study.

Clinical chemistry. Clinical chemistry determinations were made for each living animal two weeks prior to the commencement of treatment and during the study at weeks 13, 26, and 52. Jugular puncture was used to collect blood samples. The following tests or assays were performed:

Hematology - erythrocyte count, hemoglobin, total leukocyte count, hematocrit, and platelet count;

Serum Chemistry - potassium, total protein, globulin, total bilirubin, glucose, serum glutamic pyruvic transaminase, creatinine, total cholesterol, plasma cholinesterase, gamma glutamyl transpeptidase, creatine phosphokinase, prosphorus, serum glutamic oxaloacetic transaminase, blood urea nitrogen, calcium, albumin, chloride, and sodium;

Urinalysis (performed on urine collected from animals which had been food and water fasted for about 16-18 hours) - specific gravity, appearance, glucose, bilirubin, microscopic examination of sediment, volume, protein, ketones, occult blood, and reducing substances;

Differential leucocyte counts and erythrocyte and leukocyte morphology determinations were made in the control and top dose groups only since the study authors did not find major differences between the two dose groups with respect to these parameters.

Opthalmoscopy. At the initiation and at week 52 of the study, eyes of all living animals were examined with a slit lamp and a direct and indirect opthalmoscope.

Necropsy and gross pathological examination. Animals surviving the 52-week study were weighed prior to being terminated. The necropsy procedure included an examination of an animal's carcass, external surface, orifices, nasal and paranasal sinuses, cranial cavity, cervical tissues and organs, and the thoracic, abdominal, and pelvic cavities (and their respective viscera). The external and cut surfaces of the brain and spinal cord were examined after fixation.

The following absolute organ weights and relative organ weights (organ weight/body weight) were determined for animals surving the study: ovaries, brain (including brainstem), kidneys, testes with epididymis, liver (including gallbladder), and adrenals.

Histopathological exam. Tissues submitted for histopathological scrutiny were first preserved in 10% formalin and then stained with hematoxylin and eosin, or, in the case of some nerve tissues, with Kluver-Barrera luxal fast blue-stain (for myelin) or Hirano-Zimmerman Silver stain (for nerve processes). Examinations of the following tissues (obtained from each animal) were performed: pancreas, gallbladder, urinary bladder, adrenals, stomach, lung, thymus, eyes with optic nerve, pituitary, skeletal muscle, liver, kidneys, mesenteric lymph node, mandibular lymph node, bone marrow (sternum), thyroid (parathyroids), brain (fore-, mid-, hind-, including basal ganglia, pons, and medulla), skin, lesions, spleen, femur, sciatic nerve (proximal middle and distal portions), spinal cord (cervical, thoracic, lumbar, and ganglion), aorta, trachea, colon, cecum, rectum, heart, mandibular salivary glands, esophagus, duodenum, jejunum, and ileum. Also examined were the testes (with epididymis) and prostate of males and the ovaries, uterus, and mammary glands of females.

Calculations and Statistical Methods: Mean compound consumption (mg/kg/day) for each test group was calculated for weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16 and every fourth week thereafter based on the food consumption and body weight of individual animals in a particular test group during the study interval under consideration and the concentration of test material in the group's diet.

According to the study authors, the following data were statistically analyzed: clinical chemistry data (except leukocyte differentials, erythrocyte morphology, and urinalysis data), body weight changes (statistically "evaluated at initiation through weeks 13, 26, and at week 52"), and total food consumption (statistically "evaluated from the start of the study through week 52"). However, data tables containing the actual body weight changes and total food consumption values evaluated by study authors were not provided.

Statistical evaluation procedures were as follows: Levenes' test was used to determine homogeneity of variances. Data with homogeneous variances were analyzed by one way classification analysis of variance (ANOVA). Data transformations were applied, as it was considered necessary, to non-homogeneous variances. If heterogeneity of variances could not be removed, ANOVA was performed on ranked data. Dunnett's T-Test was used for control versus S-3206-treated group mean comparisons if ANOVA of untransformed or transformed data was found to be significant.

RESULTS

Group Mean Body Weights - Males: One male (#21802) in the 100 ppm dose group had an initial body weight (i.e. 11.6 kg) that was almost 3 standard deviations above the mean of the initial body weights of males in all groups (i.e. 7.66 kg $\pm$ 1.42). The selection of an animal with an initial body weight of no more than 2 standard deviations above or below this mean would have been more appropriate for the study.

In general, throughout the study, the group mean body weight of males in the 100 and 250 ppm dose groups was similar to control values (i.e. ranged from about 98 to 110% of the control). Starting at about study week 10, group mean body weight in the 750 ppm dose group began to fall below 98% of the control mean and by week 28, had declined to about 89% of the control value. It remained at about 89% to 93% of the control mean for the rest of the study.

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Body Weight Changes - Males*: When group mean body weight changes over study weeks 0 through 52 were compared, the mean body weight change in the 750 ppm dose group was only 78% of the control value while greater body weight changes were noted in the 250 and 100 ppm dose groups (respectively 96% and 86% of the control mean).

Group Mean Body Weights - Females: Throughout the study, the group mean body weight of females in the 100 ppm dose groups was close to 100% of the control value. Group mean body weight in the 250 ppm dose group was similar to that of the control group until week 24. Thereafter, it declined to about 95% of the control mean and then, generally fluctuated between 95% and 96% of the control value till the end of the study.

An earlier and eventually greater departure from control values was seen in the 750 ppm dose group. Mean body weight in this group declined from 93% of the control mean at study week 1 to 83% of the control mean by week 24. It then fluctuated between about 80% and 85% of the control value for the rest of the study.

Body Weight Changes - Females*: When mean body weight changes occurring over weeks 0 to 52 were compared, the change in the 100 ppm dose group was similar to that of the control group. However, weight gains over the course of the study were not as substantial in the 250 and 750 ppm groups where the changes in mean body weight noted were respectively 91% and 60% of the control value.

Significance of Body Weight Data: The study authors did not find any statistically significant differences in group mean body weight changes, compared to controls, in any of the S-3206-treated groups of males or females. However, in the high dose groups of males and females, the relatively smaller gains in body weight observed and the magnitude and duration of the relative decreases in mean body weight noted suggested to this reviewer that these were treatment-related effects.

Food Consumption: Group means of total food consumed over study weeks 1-52* by males in the 100, 250, and 750 ppm S-3206 dose groups and by females in the 100 and 250 ppm dose groups were about 90% of the respective control means or greater. Both males and females in the 750 ppm dose group appeared to require some time during the first four weeks of the study to adapt to the level of test material contained in their diet. The group mean of total weekly food consumption calculated for females in the 750 ppm dose group was about 83% of the control value but was not found by the study authors to be statistically different from controls. Based on the data submitted, consumption of less food does not seem to adequately account for the relatively smaller body weight change (over weeks 0-52) observed in the group of females fed 750 ppm of S-3206, nor can it be used to sufficiently explain the relatively smaller mean body weight change over weeks 0-52 observed in the group of males fed 750 ppm of S-3206.

Test Material Consumption: Group mean compound consumption, examined on a mg/kg/day basis, was found, in all groups of males and females dosed with S-3206, to peak at or slightly before week four. These peak values were respectively, for the high-, mid-, and low-dose groups of males, about 30, 11, and 4 mg/kg/day and for the high-, mid-, and low-dose groups of females about 33, 10, and 4 mg/kg/day. Compound consumption then tended to decline in all groups as the study

* Calculated by reviewer from data submitted by study authors.

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progressed. At week 52, compound consumption had dropped to about 19, 7, and 3 mg/kg/day respectively in the high-, mid-, and low-dose groups of males and to about 22, 5, and 2 mg/kg/day respectively in the high-, mid-, and low-dose groups of females. Although there were some fluctuations in intake of test material in all groups, variations were particularly large in the low dose groups.

Analysis of Test Compound in the Diet: Based on the data submitted, the amount of S-3206 in each of the test diets appeared to lie, in general, within ± 10% of the targeted amount for each dose level (detection limit 0.002 ppm).

Mortality: Only one dog, a male (#21818) in the 750 ppm dose group, did not survive the study. This animal was found dead during week 52 and it was reported that prior to death, this dog was languid, thin and exhibited clinical signs of ataxia, tremor, polypnea, and excessive salivation. Numerous gross- and histopathological findings were reported for this animal.

Clinical Parameters: Major clinical findings and behavioral changes reported for males and females in all treatment groups are presented in Tables 1 and 2 below and are discussed in the subsequent paragraphs. Tables 1 and 2 provide information about the frequency at which a given parameter was reportedly observed. Information indicating the severity of a particular occurrance was not submitted.

TABLE 1. MAJOR CLINICAL AND BEHAVIORAL FINDINGS REPORTED FOR MALE DOGS DURING STUDY WEEKS (0-53)[a,b]

	Total Number of Incidences Observed / Total Number Animals Affected per Group			
Parameter	Control	100 ppm	250 ppm	750 ppm
Tremor	0/0	0/0	160/4	1086/4
Ataxia	0/0	0/0	0/0	346/4
Languid Behavior	0/0	0/0	0/0	100/4
Emesis	24/4	22/4	19/4	28/4
Soft or Mucoid Feces &/or Diarrhea	58/4	110/4	98/4	42/4
Bloody-Appearing Feces	0/0	0/0	1/1	2/1
Alopecia	45/3	16/2	182/2	199/2
No. Animals Examined	4	4	4	3 or 4[c]

a Table constructed from data submitted by study authors.
b Terminal sacrifices were completed during week 53.
c Four animals per group were examined during weeks study weeks 0-32. Three animals per group were examined during study weeks 32-53 due to death of male dog #21818.

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TABLE 2. MAJOR CLINICAL AND BEHAVIORAL FINDINGS REPORTED FOR FEMALE DOGS DURING STUDY WEEKS (0-53)[a,b]

Parameter	Total Number of Incidences/Total Number Animals Affected Per Group			
	Control	100 ppm	250 ppm	750 ppm
Tremor	0/0	1/1	97/4	771/4
Ataxia	0/0	0/0	0/0	127/4
Convulsions	0/0	0/0	0/0	1/1
Languid Behavior	0/0	0/0	0/0	47/4
Emesis	11/4	11/3	37/4	20/4
Soft or Mucoid Feces &/or Diarrhea	80/4	36/4	108/4	40/4
Bloody-Appearing Feces[c]	0/0	0/0	3/1	22/1
Alopecia	85/2	16/1	41/2	123/2
No. Animals Examined	4	4	4	4

a Table constructed from data submitted by study authors.
b Terminal sacrifices were completed during week 53.
c Approximation; exact number was not reported.

Ataxia, tremor, alopecia, and convulsion. Incidences of ataxia and languid behavior in the 750 ppm dose groups and of tremor in the 750 ppm and 250 ppm dose groups are judged to be toxic effects related to ingestion of the test material and the dose thereof. Although the single episode of convulsion in one high-dose group female was not described, it seems likely that the incident was also a toxic effect related to test compound administration. However, the single incidence of tremor in one low dose group female was not considered to be toxicologically significant. Treatment-related increases (compared to controls) in alopecia in the groups of males given 750 and 250 ppm S-3206 were noted. However, it could not be determined from the data presented whether the cause of the alopecia involved a direct or indirect systemic effect of the test material, and/or whether it involved a local effect due to contamination of the dog's external body surface with treated food, or whether some other mechanism was operative.

Emesis. Among the groups of male dogs, there appeared to be no substantial difference in the incidences of emesis reported. However, compared to the control group, emesis occurred somewhat more frequently in females in the 250 ppm and 750 ppm dose groups, although the occurrances in these two groups were not dose-related.

Based on the information and data submitted, it is not possible to ascertain if the increased incidences of emesis observed in the mid- and high-dose groups

of females were to any extent systemic toxic effects resulting from ingestion of S-3206-containing diets. A possible complicating factor in the interpretation of the emesis data is the fact that dogs were given the test diet ad libitum. Therefore, a certain portion of the incidences of emesis reported in any group could simply have been the consequence of overeating. Emesis could have also resulted if the test material in the diet had an unpleasant taste or acted locally as a upper GI-tract irritant.

Soft or mucoid feces and/or diarrhea. A clear-cut relationship between ingestion of test material and soft feces/diarrhea could not be established. In the case of male dogs, compared to controls, there was an increased incidence of soft feces/diarrhea in groups of animals treated with 100 ppm and 250 ppm S-3206 in the diet. However, the incidence in the high dose group was less than that of the controls. Among groups of female dogs, incidences of soft feces/diarrhea in the 100 ppm and 750 ppm dose groups were at least one-half of the control incidence. Some animals appeared to have a greater tendancy than others towards soft feces/diarrhea i.e. 57 out of 110 incidences in the male 100 ppm dose group were attributed to dog number 21801, 51 out of 108 incidences in the female 250 ppm dose group were attributed to dog number 21814, and 31 out of 40 incidences in the female 750 ppm dose group were attributed to dog number 21822. Approximately twenty-two (22) instances of bloodly-appearing feces (presence of blood not confirmed clinically) were also noted for female dog number 21822, so perhaps the test material was a strong irritant in this animal. However, there were no apparent treatment-related gross- or histopathological findings in the GI-tracts of animals fed S-3206 in the diet (with the possible exception of dog #21813).

Missing body parts. One high-dose male (#21817) was reported to have some toes missing from its right front paw at the end of study week 1. A possible reaon for this occurrance was not provided by the study authors. The animal may have been responding to some external body surface irritation as its food food consumption during the first study week was not unusually low.

Clinical Chemistry: Group means were calculated using four animals/group except at week 52 when only three male dogs remained in the 750 ppm dose group.

Red blood cell counts, hemoglobin and hematocrit determinations. Relative to controls, decreases in three blood parameters, red blood cell count (RBC), serum hemoglobin (HGB), and hematocrit (HCT), were noted in the group of males to which 750 ppm of the test material had been administered. The decreases were judged to be treatment-related. At week 13, mean RBC and mean HGB were less than 90% (i.e. 88% and 87% respectively) of the corresponding control means. At that time point, the mean HCT was 85% of the control mean, a decrease that was reported to be statistically significant. By week 26, mean RBC, mean HGB, and mean HCT in the high-dose male group were respectively 85%, 84%, and 84% of the corresponding control means and these declines were all found to be statistically significant by the study authors. At week 52, mean RBC and HGB had each increased to 92% of controls, and mean HCT had increased to 89% of controls which suggested that the effects noted may have been transient. There were no apparent treatment-related differences between the appropriate control group and other groups of S-3206-treated males or groups of S-3206-treated females.

Serum glucose levels. Increases, which appeared to be treatment-related, were noted in mean serum glucose levels in both mid- and high-dose groups of

male and female dogs, compared to corresponding controls. At week 26, mean serum glucose levels in group of males given 750 ppm S-3206 in the diet were increased over the control mean by 12% . Similar increases (of 15% and 10% respectively) were also noted in the groups of females fed 250 ppm and 750 ppm of test material. The increase in the mid-dose group of females was reported to be statistically significant. By week 52, mean blood glucose levels were elevated by 13% above the control mean in the 250 ppm dose group of males and had risen to 123% of controls in the male 750 ppm dose group. The latter increase was said to be statistically significant by the study authors. The study authors also reported that statistically siginificant increases of 11% and 18% relative to controls were observed at 52 weeks in the groups of mid- and high-dose females. No treatment-related effects were apparent in the low dose group.

Other clinical findings.

GGT. Relative to controls, a statistically significant increase in serum gamma glutamyl transpeptidase (GGT) was reported to have occurred only at week 26 in the high dose group of females but, since the high dose group mean of 3 mu/ml was not that much higher than the values in the other dose groups (i.e. 0, 1, and 1 mu/ml in the control, low-, and mid-dose groups respectively) and since relatively large standard deviations were often associated with this parameter, the toxicological significance, if any, of the increase was unclear. At other weeks, GGT group means (male and female) ranged from 0 to 2 mu/ml.

Phosphorus and creatinine. Compared to controls, a statistically significant increase of 16% was reported in the serum phosphorus group mean in the 250 ppm dose group of females at week 13 and a statistically significant increase of 30% in the serum creatinine group mean was reported for the same dose group at week 26. However, a clear cut connection between treatment and the increases observed was not evident.

Other. Increases noted in a few group means were primarily the result of an elevated value in an individual animal composing the group (i.e. increases (relative to controls), of 33% in the blood urea nitrogen group mean of high-dose males at week 26 and of 145% and 19% in serum glutamic pyruvic transaminase group means of high-dose males at week 13 and 26 respectively, were primarily due to elevations observed in male dog #21818, the male that did not survive the study).

Declines of 24% and 22% compared to controls in serum glutamic oxaloacetic transaminase group means at weeks 13 and 26 in the female 750 ppm dose group were judged not to be treatment-related since toxic effects are normally asssociated with relative increases rather than decreases in this parameter.

There was no apparent affect of test material administration on the other clinical parameters which were examined in this study.

Urinalysis and Opthalmological Examination: There were no obvious treatment-related effects.

Terminal Body Weights and Absolute and Relative Organ Weights: No data from male #21818 was included in the calculation of these group means. While the terminal body weight group mean of males in the 100 and 250 ppm dose groups were similar to the control value, the group mean of the 750 ppm dose group

was about 8% lower than that of the control mean. In addition, terminal body weight group means in the low-, mid-, and high-dose groups of females were about 100%, 94%, and 81% of the control mean respectively. As was indicated in the discussion in a previous section on body weights, the relative decreases in the high dose group mean body weights of males and females were judged to be treatment related.

There were no differences in absolute or relative organ weight group means that could definately be attributed to test compound administration. Although the study authors found a statistically significant increase of 21% compared to controls in the mean relative kidney weight of females in the 750 ppm dose group, the increase appeared to be a reflection of the comparative decrease in the terminal body weight mean for this group rather than to a treatment-related affect on kidney weight. The mean absolute kidney weight of the female high dose group was similar to that of controls.

Gross- and Histopathological Examination: With the possible exception of dog #21818, there did not appear to be any gross- or histopathological findings in any of the S-3206-treated animals which could be attributed to test material administration.

Dog #21818. This animal had multiple gross and histopathological lesions, although nothing seemed to be unusal about this male dog prior to the beginning of the study and during the first couple of study weeks based on an inspection of body weight, food consumption, and clinical data, etc.

Included in the extensive list of gross pathological finding were: soft brain, a dark, enlarged and congested liver (all lobes), enlarged lymph nodes, ulcerations and erosions of the oral cavity and perforations of the tongue, skin sores and multifocal alopecia, pale kidneys (inner cortex of both) and pale spleen, dark focus in stomach (diffuse area in pyloric region), dark lungs (all lobes), small thymus, and gas-filled and distended intestines.

Included in the list of histopathological findings were: adrenal congestion and hemorrhage, pulmonary edema and congestion , epicardial hemorrhage, liver congestion, stomach congestion and hemorrhage, kidney congestion decreased levels of pancreatic zymogen, decreased spermatogenesis with focal tubular atrophy, prostate atrophy and hypoplasia, thymus atrophy and fibrosis, lymphoreticular hyperplasia and lymph node congestion and hemorrhage, multiple skin lesions (including acanthosis, hyperkeratosis, congestion, hemorrhage, chronic active inflamation, necrosis, and imbedded hair shafts), multiple lesions of the oral cavity (including erosion, ulceration, chronic active inflamation, acanthosis, hyperkeratosis, necrosis, and bacterial infection).

The study authors indicated that they could not determine whether or not test material administration "contributed to the development" of skin and oral cavity lesions. However, somewhat contradictorily, they also stated in their report that "no compound-related gross pathological findings were observed ....[and] no compound-related histomorphological alterations were induced by S-3206 T. G. under the conditions of the study". It is the opionion of this reviewer that it cannot be determined from the data submitted if the test chemical contributed to or was associated with the the development of the multifacited pathological picture presented by dog #21818, particularly since corroborating gross and histopathological evidence from other S-3206-treated animals is lacking.

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COMMENTS

1. A particular weakness of this study was that animals were given the test diet ad libitum. Dogs have a tendancy to overeat if given the opportunity, but the result is often an overtaxation of the GI system such that GI upset, irritation, and emesis follow. At the very least, overeating puts an additional stress on the animal and the results of it may needlessly interfere with, complicate, or confuse the interpretation of data obtained from the study. A better and more realistic study design could have incorporated a fixed quantity of food per animal per day which would include the test material. The amount of test material in the food could then be adjusted on a mg food/kg body weight/ day basis as the study progressed.

2. Since food and therefore test material was given ad libitum, the study authors should have described in detail how the amount of food and test material ingested by each dog was measured.

3. It was reported that the test material was determined to be stable for a week, however analysis of some of the weekly diet samples took place as much as 30 days after the sample was taken.

4. Data tables containing the actual body weight changes and total food consumption values evaluated by the study authors were not provided.

5. A few comments about reporting of the study should also be made:

a. The way in which incidence tables and appendices for clinical signs were structured made inter-dose group comparisons difficult, especially if many incidences of a particular parameter occurred during the study; Study authors should display data accurately and completely, yet tables and appendices should be set up in such a way as to facilitate the review process, not hamper it.

b. Regarding clinical sign incidence tables and appendices: it was often difficult to physically line up an incidence with an individual animal number, even with the aid of a grid;

c. It was sometimes difficult to track down the meanings of abbreviations. i.e. some of the abbreviations used in tables or appendices were not defined therein but were defined elsewhere in the study report. Sometimes the abbreviation used was not defined at all. In one case, in Appendix 11, the abbreviation "N" was used but the only N defined in the accompanying key referred to the presence of a neoplasm. However it became evident that the study authors meant that the tissue had not been examined. In another case, some codes apparently defined in the Gross Pathology Appendix were used in the in the Histopathology Appendix but were not defined therein.

6. It was somewhat puzzling as to why terminal body weights listed in Appendix 10 were lower than the corresponding weights measured for animals at week 52 and reported in Appendix 2. The differeces between the weights in the the two appendices did not seem to be readily accounted for by a rounding procedure.

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CONCLUSION

Despite the foregoing comments, based on the data submitted, there appears to be enough evidence to support a systemic NOEL for S-3206 of 100 ppm in this study. There were no apparent effects of test material administration at this dose. The one incidence of tremor found in the 100 ppm dose group was not considered to be toxicologically significant and a clear-cut relationship between ingestion of test material and the increased incidence of soft or mucoid feces/diarrhea noted for males in this group could not be established. However, the numerous incidences of tremor observed in male and female dogs in the 250 ppm dose group were clearly compound related and therefore the LEL for this study is set at 250 ppm.

Core Classification: Minimum.